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Title	**Statistical Analysis Plan (SAP)**		

Prevention and early treatment of the long term physical effects of COVID-19: a randomised clinical trial of resistance exercise. CISCO-21

STATISTICAL ANALYSIS PLAN (SAP)

Study Title:	Prevention and early treatment of the long term physical effects of COVID-19: a randomised clinical trial of resistance exercise.
Short Title:	CISCO-21
IDs:	Sponsor ID: GN20CA537 Funder ID: COV/LTE/20/10 IRAS number: 294299 ISRCTN number: NCT04900961
Sponsor:	NHS Greater Glasgow & Clyde
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		Signature	Date
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1. INTRODUCTION

1.1. STUDY BACKGROUND

Many patients who have had COVID-19 describe persisting health problems after their infection. Long COVID has been defined as signs and symptoms which develop during or following a COVID-19 infection, which continue for more than 12 weeks and are not explained by an alternative diagnosis. Symptoms in long COVID patients include breathlessness, fatigue, and chest pain. COVID-19 infection, particularly where hospital admission is required, can lead to weight loss and muscle wasting, which can contribute to worse outcomes. Muscle strengthening (resistance-based) exercise could improve outcomes in the long term. Muscle mass is a strong predictor of prognosis in many chronic conditions, the main method to improve muscle mass is through resistance exercise. This approach can be adapted to the capability of an individual with little equipment required. There is a general lack of evidence-based medicines for patients with persisting symptoms following COVID-19. The CISCO-21 study aims to develop and test a lifestyle intervention which could be helpful to patients with persisting symptoms following COVID-19 infection.

1.2. STUDY OBJECTIVES

The objectives of the study are to:

- Undertake a clinical trial of pragmatic resistance-based exercise in addition to standard care versus standard care only to prevent and treat persisting symptoms following COVID-19 infection.

- Rapidly translate and disseminate research findings.

- Develop a national platform for rapid, multicentre clinical trials post-COVID-19.

The research questions are:

- Does resistance-based exercise intervention improve functional capacity and health status post-COVID-19?

- Do the results of this trial elucidate mechanisms of disease in Long COVID?

- Is a national clinical trials platform for post-COVID patients in NHS Scotland feasible?

1.3. STUDY DESIGN

A randomised, controlled, open-label, parallel group clinical trial.

1.4. RANDOMISATION

Participants are recruited from three sites: Queen Elizabeth University Hospital (QEUH), Glasgow Royal Infirmary (GRI), and Ninewells Hospital. Patients who met the eligibility criteria and provided written informed consent were randomised to either standard care or

resistance-based exercise in addition to standard care. Randomisation was stratified by clinical strata groups A, B, and C (see study population), history of COVID-19 pneumonia, age, sex, and site.

1.5. Sample Size and Power

The proposed sample size for the main study was 240 randomised participants, with 120 in each randomised group. The minimum clinically important between-group difference in the ISWT at 3 months is 46 metres, standard deviation 105. The sample size for 80% power at a 5% significance level with no loss to follow-up would be a minimum of 85 participants in each randomised group. The proposed sample size of 120 patients per group allows for loss to follow-up and incomplete data.

1.6. Statistical Analysis Plan (SAP)

1.6.1. SAP Objectives

The objective of this SAP is to describe the analyses to be carried out for the CISCO-21 final analysis.

The current version of the protocol at the time of writing is version 6.0 dated 11/01/2024. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. This will be documented as part of the Robertson Centre Impact Assessment process.

1.6.2. General Principles

This SAP is based on intention to treat principles. For tables summarising collected data, categorical variables will be presented with a count of observed and missing observations, and a count and percentage for each category. Numerical data will be presented with a count of observed and missing observations, as well as mean, standard deviation, median, Q1, Q3, and minimum and maximum values (unless stated otherwise). The analysis will focus on estimations of treatment effect differences with 95% confidence intervals and p-values. Where data are not Normally distributed, standard transformations will be applied to achieve approximate Normality in the model residuals.

1.6.3. Additional Analyses To Those Specified In Study Protocol

There are currently no plans to carry out any additional analyses. If any additional analyses are to be performed, a log of these will be kept with details of the programs written and results documents produced.

1.6.4. Protocol Deviations

This SAP has been written to be consistent with the protocol. A listing with details of protocol violators will be made available within the study database prior to lock.

1.6.5. SOFTWARE

Analyses will be conducted using R version 4.2.3 or higher, with the version of R used included in statistical output documents.

2. ANALYSIS

2.1. STUDY POPULATIONS

Potential study participants are patients with confirmed COVID-19 who are either recovering in hospital, have been discharged from hospital, or not admitted to hospital, and who have persisting symptoms for at least 4 weeks. Patients are classified according to their clinical presentation into one of three groups:

A) Non-hospitalised (treatment group): Positive diagnosis with persisting symptoms for at least 4 weeks from onset of symptoms leading to medical review (e.g. at A&E or a community COVID hub), but not admission.

B) Hospitalised (treatment group): Positive diagnosis with post-discharge, persistent symptoms for at least 4 weeks following symptom onset.

C) Hospitalised (prevention group): Positive diagnosis, in convalescent phase in hospital.

Groups A and B are the target population for treatment of Long COVID, while group C is the target population for prevention of Long COVID.

The inclusion criteria are:

- At least one of the following:
    - Virology PCR positive laboratory diagnosis, or positive point of care test for COVID-19
    - Positive lateral flow test (confirmation from notes or participant)
    - Positive COVID antibody test.
- Persistent symptoms for at least four weeks from onset of symptoms (group A and B only).
- Presentation type consistent with one of group A, B, or C.

The exclusion criteria are:

- Inpatient physiotherapy as part of current standard care post-ICU.
- No expectation of being able to walk within 3 months.

- Unable to provide informed consent.
- Unable to comply with study protocol.
- Known pregnancy.

Descriptive analyses of the study population will be provided, including the number of patients screened and randomised, summaries of inclusion/exclusion criteria, as well as details of why participants were not randomised. The screened population is all participants who attended the screening visit as reported in the screening log, while the randomised population is all participants who went on to participate in the trial. The full analysis set will consist of the randomised population who attended both study visits A CONSORT diagram will be created to illustrate progression of the participants through the study.

2.2. STUDY STATUS

At the time of writing, there are 233 participants randomised, and no further participants will be recruited or randomised. Follow-up is ongoing. Study status will be presented in tables with numbers who completed the study, withdrew, and were lost to follow-up. Counts for how many patients attended each visit will also be presented.

2.3. BASELINE CHARACTERISTICS

The following information will be summarised as a whole and in relation to randomised group for participants at baseline:

- Demographics (including age, sex, ethnicity, healthcare worker status, ICU worker status, and smoking status)
- Clinical presentation (group A, B, or C, as described in Study Population)
- COVID-19 details (including details of index COVID episode care (diagnosis and treatment), Index Illness severity scores (ISARIC 4c COVID Risk Score, WHO Clinical Severity Score), post-COVID lung disease, ACS associated with COVID-19, vaccination status, and re-infection)
- Medical history (cardiovascular and respiratory), and clinical status;
- Pre-existing CV therapy
- Charlson Comorbidity index
- MRC Dyspnoea Score
- Vital signs (including heart rate, rhythm, BP, height, weight, waist circumference, and oxygen saturation);
- Cardiovascular risk factors and risk score (QRISK3, Heart Age Score);

- Routine blood samples (as per standard of care);
- Spirometry (peak expiratory flow rate, forced vital capacity, and forced expiratory volume in one second);
- Handgrip strength (peak force in kilograms);
- Short Physical Performance Battery;
- Accelerometer (Glasgow sites only, QUEH and GRI);
- Patient recorded outcome measures (including EuroQol-5D, brief Illness Perception Questionnaire, Duke Activity Status Index, short form International Physical Activity Questionnaire, Fatigue Severity Scale, Visual Analog Fatigue Scale, and DePaul Symptom Questionnaire);
- Frailty measures (Fried 5 criteria phenotype and the clinical frailty scale);
- Incremental Shuttle Walk Test;
- Current exercise capacity (Exercise Dose category - bedbound, up-to-sit, ambulatory).

For a supplementary document these characteristics may also be summarised according to the clinical presentation group of participants.

2.4. Efficacy Outcomes

2.4.1. Primary Outcome

The primary outcome is the incremental shuttle walk test (ISWT) at 3 months. This is a validated measure of functional capacity, with evidence of being responsive to rehabilitation interventions. This will be summarised overall and by randomised treatment group at baseline, 3 months, and the change between these two time points. The outcome will be analysed using a linear regression model which will be adjusted for baseline value of ISWT, the randomised treatment group, clinical strata groups A, B, and C (see study population), history of COVID-19 pneumonia, age, and sex. If the outcome is non-Normally distributed, standard transformations will be used to improve model fit. To check the fit of this model, a Normal Q-Q plot will be produced and inspected, and covariates will be assessed for collinearity.

2.4.2. Secondary Outcomes

1) The secondary outcomes are listed below. These will be summarised in the overall study population and randomised treatment groups. Spirometry (measurements taken are listed in Baseline Characteristics).

2) Handgrip strength.

3) Short Physical Performance Battery (SPPB).

4) EQ-5D, Patient Health Questionnaire (PHQ), illness perception (brief IPQ), Duke Activity Status Index (DASI), International Physical Activity Questionnaire (IPAQ-SF), fatigue questionnaires, and MRC dyspnoea score.

5) Frailty, as assessed by the Fried frailty phenotype (five criteria – weight loss, exhaustion, grip strength, low physical activity, and slow walking pace) and the Clinical Frailty Scale (both current frailty and the best frailty within the previous month).

6) Episodes of care (primary, secondary, physiotherapy, rehabilitation). These events will be summarised but analysis of this outcome is not covered by this SAP.

7) Hospitalisation for any reason. Hospitalisation events will be summarised but analysis of this outcome will be documented separately.

Where continuous data are approximately Normally distributed, and baseline levels are available for adjustment, baseline-adjusted linear regression models (which are also adjusted for randomisation group, clinical strata groups A, B, and C, history of COVID-19 pneumonia, age, and sex) will be used to analyse these outcomes. For continuous data which are not Normally distributed, standard transformations will be used to achieve approximate Normality prior to analysis. Checks of the model fit will include inspection of Normal Q-Q plots and assessing collinearity.

Ordinal outcomes (e.g. frailty measures) will be analysed using an ordinal logistic regression model. The proportional odds assumption will be checked using a likelihood ratio test which compares the model used to one where treatment group is a nominal effect. The model will be summarised with odds ratios and corresponding 95% confidence intervals. To check the fit of the models, plots of observed versus fitted values be inspected.

2.4.3. EXPLORATORY OUTCOMES

The exploratory outcomes are listed below. Each of these will be analysed with an appropriate regression method unless otherwise stated.

1) Exercise dose achieved as detailed by activity level attained, and within-subject change from baseline. This information is only available for subjects randomised to the intervention so the outcome will be presented with descriptive analysis for the intervention group only.

2) Vital parameters of cardio-respiratory function (e.g. oxygen saturation, heart rate, respiratory rate) at baseline and follow-up.

3) Adherence with exercise. This information is only available for subjects randomised to the intervention so the outcome will be analysed for the intervention group only.

4) Accelerometry (Glasgow sites only). Note that as this outcome relates to a substudy, the analysis may be reported separately to the main study publication.

5) Biobank tissue samples for biomedical research. Note that this outcome is not covered by this SAP.

6) Optional observational substudy of small vessel function using myography in arterioles isolated from gluteal skin biopsies and laboratory analysis of adipose tissue, cells, and molecules from the biopsy. Note that this outcome is not covered by this SAP.

7) Exploratory graphical analyses of COVID-19 immune serology (as assessed at 3 month follow-up) and its association with illness severity, as reflected by biomarkers (e.g. NTproBNP, HbA1C, BMI), functional markers (e.g. handgrip strength, SPPB, spirometry), and patient reported outcome measures (e.g. EQ-5D, iPAQ, DASI).

2.4.4 Sub-group Analysis

The primary outcome analysis will be repeated to assess if the treatment effect varies between levels in the following subgroups:

- Clinical presentation groups
- Sex
- SIMD decile
- Ethnic group
- COVID-19 serology.

2.5. Safety Outcomes

2.5.1. Premature Withdrawal

Patient withdrawal is recorded in the eCRF. Dates and reasons for withdrawal from the intervention or long-term follow-up are recorded. A listing will be created which will include details of withdrawals, and withdrawal data will be summarised as part of the final report.

2.5.2. Serious Adverse Events

Serious adverse events are captured within the eCRF for review by the chief investigator. Such events have date of event, level of severity, and diagnosis recorded. Any concomitant medications, relevant tests, or medical history may also be recorded. There are no specific adverse events of interest for this study. A listing will be created including details of all SAEs, and SAE data will be summarised and presented as part of the final report, split by treatment group.

3. DATA CONVENTIONS

A separate assumptions document detailing data rules (e.g. partial dates, missing data imputation) will be created and saved to the following location: \\RCB-STORAGE\filestore\Studies\CISCO21\StudyDiary\StatsDocs\Assumptions.

4. TABLES AND FIGURES

A table shells document will be prepared and stored in the following location: \\RCB-STORAGE\filestore\Studies\CISCO21\StudyDiary\StatsDocs\SAP\TableShells.

5. DOCUMENT HISTORY

This is the first version (v1.0) of this document (initial creation).

Certificate Of Completion

Envelope Id: AF5020A8A0EF446D839B4F824F00D5A0
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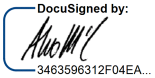
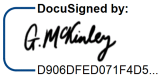
Alex McConnachie alex.mcconnachie@glasgow.ac.uk Professor of Clinical Trial Biostatistics University of Glasgow Security Level: Email, Account Authentication (None) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	DocuSigned by:  3463596312F04EA... Signature Adoption: Uploaded Signature Image Using IP Address: 130.209.6.41	Sent: 07-11-2024 | 08:52 Viewed: 07-11-2024 | 08:53 Signed: 07-11-2024 | 08:53 Freeform Signing
Gemma McKinley gemma.mckinley@glasgow.ac.uk Junior Biostatistician University of Glasgow Security Level: Email, Account Authentication (None) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	DocuSigned by:  D906DFED071F4D5... Signature Adoption: Uploaded Signature Image Using IP Address: 130.209.6.41	Sent: 07-11-2024 | 08:52 Viewed: 07-11-2024 | 08:52 Signed: 07-11-2024 | 08:53 Freeform Signing

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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Signing Complete	Security Checked	07-11-2024 | 08:53

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Payment Events	Status	Timestamps